

Att'y Dkt. No.: UCSF-129  
USSN: 09/817,360

<b>DECLARATION OF MICHAEL S. GERMAN UNDER 37 C.F.R. § 1.132</b>	Attorney Docket	UCSF-129CIP
	First Named Inventor	Michael S. German
	Confirmation Number	2345
	Application Number	09/817,360
	Filing Date	March 20, 2001
	Group Art Unit	1635
	Examiner Name	Brian Whiteman
	Title: <i>Production of pancreatic islet cells and delivery of insulin</i>	

Dear Sir:

1. I, Michael S. German, declare and say I am a resident of the State of California.  
My residence address is 343 Glenwood Ave, Daly City, CA 94015.
2. I hold a B.A. degree in Biochemistry, which I received from the Harvard University, Cambridge MA, in 1979. I further hold an M.D. degree, which I received from the Southwestern Medical School, Dallas, TX, in 1983. I completed my residency and fellowship training at the University of Arizona Affiliated Hospitals.
3. I am an Associate Professor in the Department of Medicine and Hormone Research Institute at the University of California, San Francisco (UCSF) and Clinical Director of the UCSF Diabetes Center.
4. I have worked in the field of pancreas development for over 10 years and have published over 40 articles in the fields of pancreas development, insulin production, and transcription factors. Details of my career and publications may be found in my *curriculum vitae*, provided herewith.

Atty Dkt. N .: UCSF-129  
USSN: 09/817,360

5. I have been asked to a) provide information regarding my laboratory's use of neuroendocrine bHLH transcription factors to make insulin producing cells, and b) provide my opinion of the following question: would one of skill in the art would expect to be able to successfully perform the claimed *in vitro* methods using neuroendocrine bHLH transcription factors other than neurogenin3, neuroD1 and mash1.
6. It is my understanding that '360 patent application is to be viewed from the standpoint of one of ordinary skill in the art in the relevant field (a "Skilled Person") at the time of filing of the '360 patent application. The '360 patent application was filed on March 20, 2001 and relates to the field of gene expression and organ development. I would expect a Skilled Person in the relevant field of gene expression, immediately prior to and up to March 2001 (the "relevant period") to have been represented by a scientist with a Ph.D. degree and two years of postdoctoral experience. I consider that such a Skilled Person would have the ability to perform gene expression assays, and perform phylogenetic analysis of transcription factors without inventive effort.
7. Since prior to and during the relevant period I a) regularly attended external and internal meetings at which Skilled Persons presented their research, b) regularly read and reviewed scientific literature in which Skilled Persons presented their research, and c) was head of a laboratory in which several Skilled Persons have received training, I believe that I am qualified by training and experience to address what a Skilled Person would have understood from a reading of the '360 patent application.

Atty Dkt. No.: UCSF-129  
USSN: 09/817,360

8. The following remarks constitute the basis for my opinion that: Based on the information provided in the '360 patent application, one of skill in the art would expect to be able to successfully perform the claimed *in vitro* methods of making insulin-producing cells.
9. In my laboratory, using the methods described in the '360 patent application, we made insulin-producing cells *in vitro* using the class B bHLH islet transcription factors *neurogenin3*, *neuroD1* and *mash1*. Data corresponding to this statement are provided herewith, in Appendix A, Appendix B, Appendix C.
10. Appendix A is a polyacrylamide gel stained for DNA products of RT-PCR experiments showing expression of insulin (the eighth panel down), in *in vitro* cultured mPAC cells (L20 and L4S2), using adenovirus vectors to express several transcription factors (e.g. *ngn3*, *neuroD1*, *Mash1*, and *myoD*). In detail, cells were treated with recombinant adenoviruses encoding LacZ or the class B bHLH proteins *neurogenin3*, *NeuroD/BETA2*, *Mash 1* and *MyoD*. Levels of key pancreatic developmental transcription factors and islet specific protein mRNAs, e.g., insulin, were analyzed by RT-PCR 48 h after viral treatment. Tissue cultured cells or freshly isolated mouse islets were used as positive controls. PCR cycle numbers were 35-38 or 30 for the actin control.
11. Appendix B is another gel stained for DNA products of RT-PCR. When the RT-PCR experiments of Appendix A were repeated, this time increasing the number of PCR cycles, insulin production was detected in *mash1* expressing cells. PCR cycle number was 38. Only results from L20 cells are shown.

Atty Dkt. No.: UCSF-129  
USSN: 09/817,360

12. Appendix C is a polyacrylamide gel stained for DNA products of RT-PCR experiments showing expression of insulin, in liver cells harvested from adult mice and cultured *in vitro*, using adenovirus vectors to express transcription factors (e.g. *ngn3* and *neuroD1*). In detail, rat livers were dispersed into individual cells and the cells were separated on a size gradient. The oval cell fractions were cultured *in vitro* and treated with recombinant adenoviruses encoding LacZ or the class B bHLH proteins *neurogenin3*, *NeuroD/BETA2*. Levels of insulin mRNAs was analyzed by RT-PCR 48 h after viral treatment. Freshly isolated mouse islets were used as positive controls. PCR cycle numbers were 34 for insulin and 30 for the actin control.
13. These results establish that, using the methods described in the '360 patent application, the transcription factors *neurgenin3*, *neuroD* and *Mash1*, can be successfully used in methods of making insulin-producing cells *in vitro*.
14. With respect to the question of how representative these transcription factors are, I state the following: In my opinion, these data are sufficient to show that a number of different types of neuroendocrine class bHLH transcription factors facilitate production of insulin-producing cells *in vitro*. *Neurogenin3*, *neuroD1* and *mash1* are representative of the broader class of neuroendocrine class B bHLH transcription factors exemplified in Fig. 11 of the '360 patent application. As shown in Fig. 11, *ngn3* is placed in the first subgroup (the neurogenins: *ngn3*, *ngn1* and *ngn2*), *neuroD1* is placed in the second subgroup (the neuroDs: *neuroD1*, *neuroD2*, *neuroD4* and *math2*), and *mash1* is placed in the third subgroup (the mash factors: *mash1* and *mash2*). Since phylogenetically closely related transcription factors typically have similar functions and we have provided a single working example of each subgroup of neuroendocrine class B bHLH proteins, one of skill in the art would recognize that the

Atty Dkt. No.: UCSF-129  
USSN: 09/817,360

group of neuroendocrine class B bHLH transcription factors exemplified in Fig. 11.  
could be successfully used in the claimed methods.

15. It is therefore my opinion that one of skill in the art would expect that other members of the class of neuroendocrine class B bHLH transcription factors could be successfully used to produce insulin-producing cells in vitro.

16. I, Michael S. German, hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title XVIII of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

6/16/03  
Date

  
Michael S. German, M.D.

F:\DOCUMENT\UCSF\129CIP\Declaration German 1.132.doc

# APPENDIX A

B.

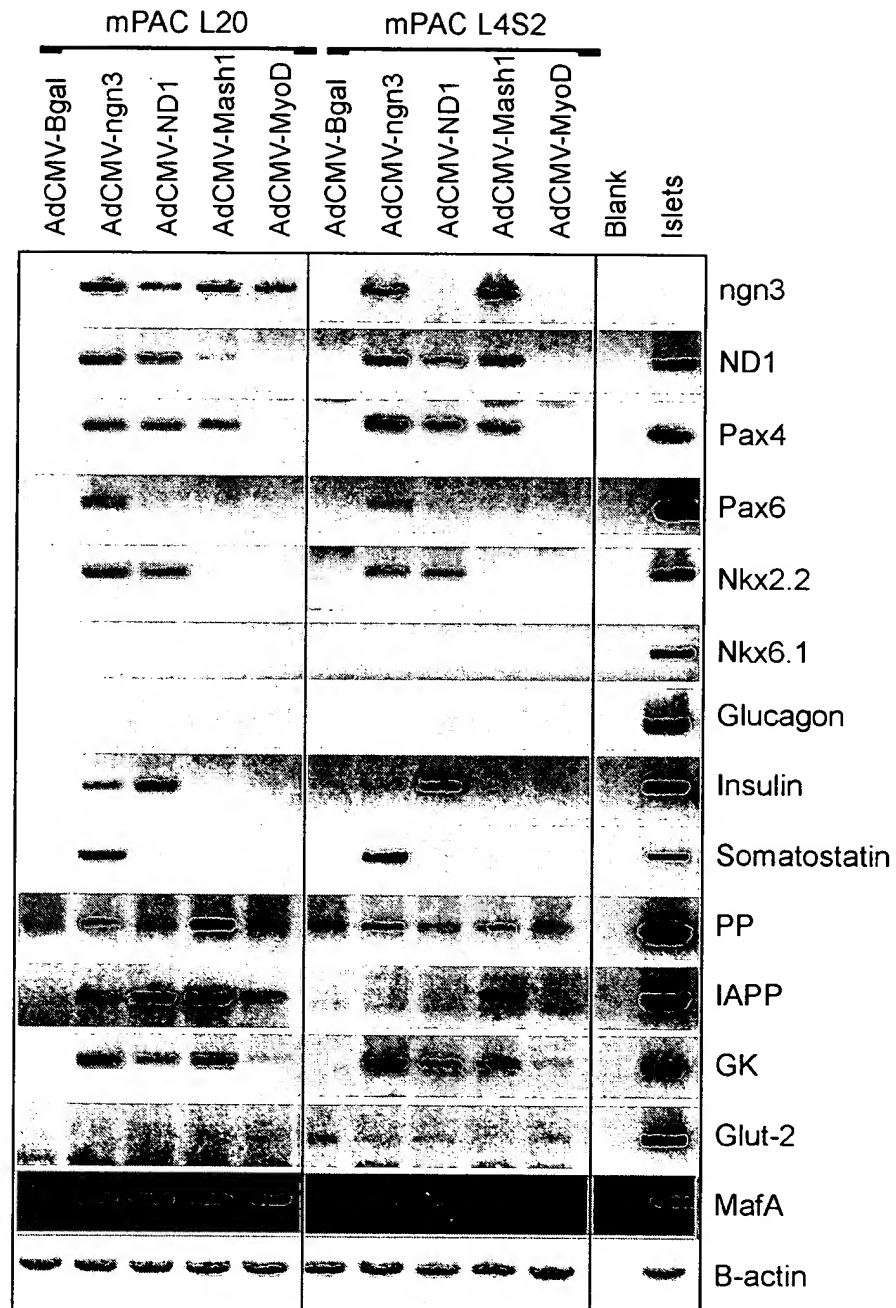
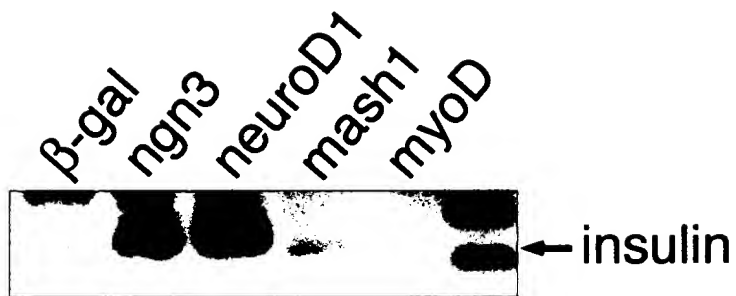
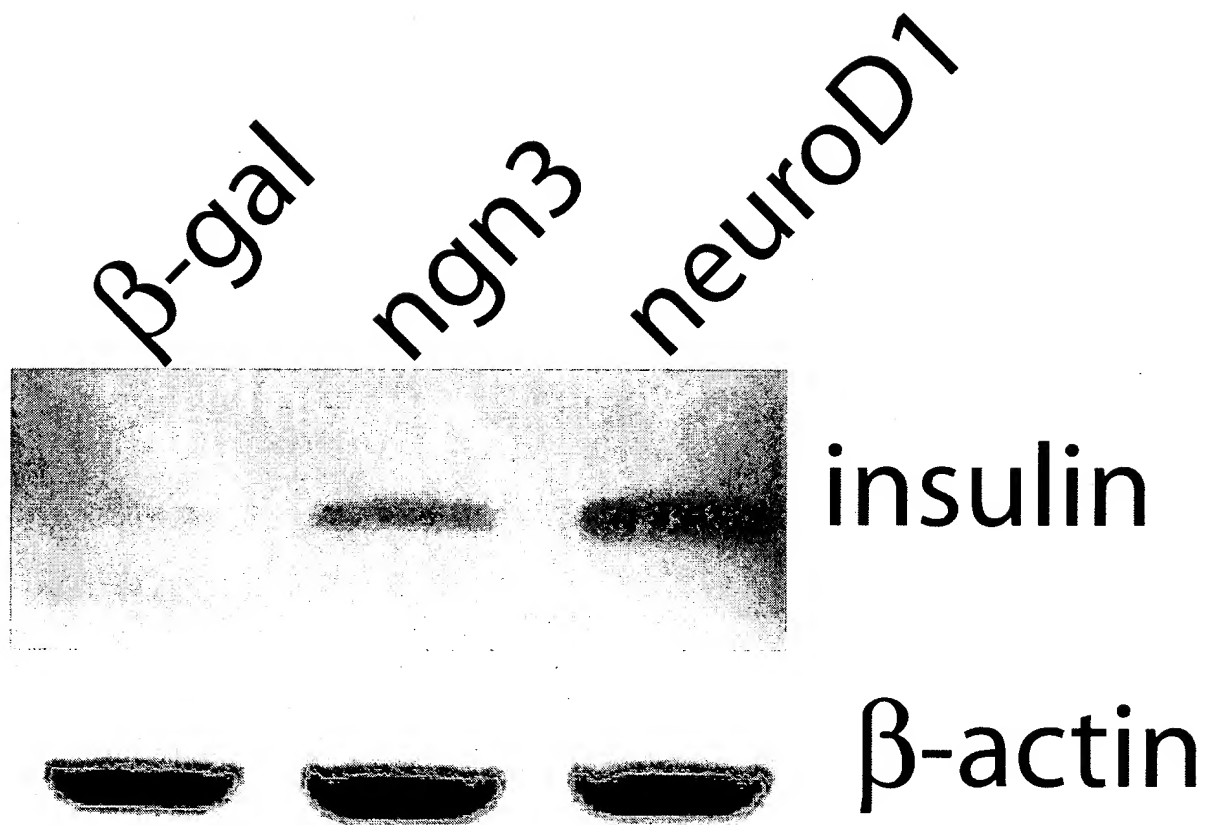


FIGURE 3B

## APPENDIX B



APPENDIX C



## CURRICULUM VITAE

**Michael Scott German**

### Present Address:

Home: 343 Glenwood Ave  
Daly City, CA 94015

Telephone: (650) 992-9070

Work: Hormone Research Institute  
University of California  
San Francisco, CA 94143-0534  
Telephone: (415) 476-9262  
Fax: (415) 731-3612  
email: [german@biochem.ucsf.edu](mailto:german@biochem.ucsf.edu)

### EDUCATION

Harvard University, Cambridge, MA	B.A.	1975-79
Southwestern Medical School, Dallas, TX	M.D.	1979-83

### EMPLOYMENT

1983-86	Internal Medicine Internship and Residency University of Arizona Affiliated Hospitals, Tucson, AZ
1986-87	Clinical Endocrinology and Metabolism Fellowship University of California, San Francisco, CA
1987-90	Research Fellowship Hormone Research Institute, University of California, San Francisco, CA
1990-93	Adjunct Assistant Professor of Medicine Hormone Research Institute, University of California, San Francisco, CA
1993-99	Assistant Professor in Residence Department of Medicine and Hormone Research Institute, UCSF, CA
1999-	Associate Professor in Residence Department of Medicine and Hormone Research Institute, UCSF, CA
2000-	Associate Director, UCSF Diabetes Center
2001-	Clinical Director, UCSF Diabetes Center

### AWARDS

Arizona College of Physicians Clinical Vignette Award 1986.  
National Institutes of Health National Research Service Award 1989-1991.  
Juvenile Diabetes Foundation Career Development Award 1991-1994.  
Kenneth R. Crispell Lecture, University of Virginia 2002  
Kroc Lecture, University of Alabama 2003

### LICENSES and SPECIALTY CERTIFICATION

California and Texas state medical licenses.  
American Board of Internal Medicine certification 1986.  
Endocrinology board certification 1991.

### MEMBERSHIPS

Endocrine Society  
American Diabetes Association  
Juvenile Diabetes Research Foundation  
Western Society for Clinical Investigation  
American Society for Clinical Investigation

## **EDITORIAL BOARDS**

*Diabetes Technology and Therapeutics*  
*Journal of Biological Chemistry*

## PUBLICATIONS

1. German, M. and Syvanen, M. Incompatibility between bacteriophage lambda and the sex factor F. *Plasmid* 8:207-210 (1982).
2. German, M. and Karam, J. Strict metabolic control and progression of incipient diabetic nephropathy. *Lancet* 87:8538 (Letter) (1988).
3. German, M., Moss, L.G. and Rutter, W.J. Regulation of insulin gene expression by glucose and calcium in primary islet cultures. *J. Biol. Chem.* 265:22063-22066 (1990).
4. German, M., Blonar, M., Nelson, C., Moss, L.G., and Rutter, W. Two related helix-loop-helix proteins participate in separate cell-specific complexes that bind the insulin enhancer. *Molecular Endocrinology* 5:292-299 (1991).
5. German, M., Moss, L.G., Wang, J., Rutter, W.J. The insulin and islet amyloid polypeptide genes contain similar cell-specific promoter elements that bind identical  $\beta$ -cell nuclear complexes. *Mol. Cell. Biol.* 12:1777-1788 (1992).
6. German, M., Wang, J., Chadwick, R., Rutter, W. J. Synergistic activation of the insulin gene by a LIM-homeodomain protein and a basic helix-loop-helix protein: building a functional insulin minienhancer complex. *Genes & Dev.* 6:2165-2176 (1992).
7. German, M. Glucose sensing in pancreatic islet  $\beta$ -cells: the key role of glucokinase and the glycolytic intermediates. *Proc. Natl. Acad. Sci. USA* 90:1781-1785 (1993).
8. German, M. Insulin gene structure and regulation. in *Molecular Biology of Diabetes* (ed. Draznin, B., and Leroith, D.) Humana Press, Totowa N.J. (1994).
9. German, M. and Wang, J. The insulin gene contains multiple transcriptional elements that respond to glucose. *Mol. Cell. Biol.* 14:4067-4075 (1994).
10. Rudnick, A., Ling, T., Odagiri, H., Rutter, W., German, M. Pancreatic islet  $\beta$ -cells express a diverse set of homeobox genes. *Proc. Natl. Acad. Sci. USA* 91: 12203-12207 (1994).
11. German, M., Wang, J., Fernald, A., Espinosa, R., Le Beau, M., Bell, G. Localization of the genes encoding two transcription factors, *Imx-1* and *cdx-3*, regulating insulin gene expression to human chromosomes 1 and 13. *Genomics* 24: 403-404 (1994).
12. Kennedy, G., German, M., Rutter, W. The minisatellite in the diabetes susceptibility locus IDDM2 regulates insulin transcription. *Nature Genetics* 9: 293-298 (1995).
13. German, M., Ashcroft, S., Docherty, K., Edlund, H., Edlund, T., Goodison, S., Imura, H., Kennedy, G., Madsen, O., Melloul, D., Moss, L., Olson, K., Permutt, A., Philippe, J., Robertson, R. P., Rutter, W. J., Serup, P., Stein, R., Steiner, D., Tsai, M.-J., Walker, M. D. The insulin gene promoter: a simplified nomenclature. *Diabetes* 44:1002-1004 (1995).
14. Tsaur, M.-L., Menzel, S., Lai, F.-P., Espinosa, R., Concannon, P., Spielman, R., Hanis, C., Cox, N., LeBeau, M., German, M., Jan, L., Bell, G., Stoffel, M. Isolation of a cDNA clone encoding a KATP-channel-like protein expressed in insulin secreting cells, localization of the human gene to chromosome band 21q22.1, and linkage studies with NIDDM. *Diabetes* 44:592-596 (1995).
15. Stoffel, M., Tokuyama, Y., Trabb, J., German, M., Tsaur, M.-L., Jan, L., Polonsky, K., and Bell, G. Characterization of a rat ATP-regulated potassium channel-like protein, KATP2: sequence, tissue distribution, and decreased expression in pancreatic islets of diabetic animals.

*Biophys. Biochem. Res. Com.* 212:894-899 (1995).

16. Kennedy, G. and German, M. Insulin gene regulation. in *Diabetes Mellitus: a Fundamental and Clinical Text* (ed. LeRoith, D., Olefsky, J., and Taylor, S.) Lippincott-Raven Pub., Philadelphia, PA (1996).

17. Odagiri, H., Wang, J., German, M. Function of the human insulin promoter in primary islet cultures. *J. Biol Chem.* 271:1909-1915 (1996).

18. Collins, A., German, M., Jan, N., Jan, L., Zhao, B. A strongly inwardly rectifying K<sup>+</sup> channel that is sensitive to ATP inhibition. *J. Neurosci.* 16:1-9 (1996).

19. Sander, M. and German, M. The  $\beta$ -cell transcription factors and development of the pancreas. *J. Mol. Med.* 75:327-340 (1997).

20. Inoue, H., German, M., Veile, R., Rudnick, A., Helms, C., Donis-Keller, H., Permutt, M. A. Isolation, characterization, and chromosomal mapping of the human Nkx6.1 gene, a new pancreatic islet homeobox gene. *Genomics* 40:367-370 (1997).

21. Wang, J., Shen, L., Najafi, H., Kolberg, J., Matschinsky, F., Urdea, M., German, M. Regulation of insulin preRNA splicing by glucose. *Proc. Nat. Acad. Sci. USA* 94:4360-4365 (1997).

22. Iannotti, C., Inoue, H., Bernal, E., Aoki, M., Yukio, T., Liu, L., Donis-Keller, H., German, M., Permutt, M. A. Identification of a human LMX1 (LMX1.1)-related gene, LMX1.2: tissue-specific expression and linkage mapping on chromosome 9. *Genomics* 46:520-524 (1997).

23. Johnson, J., Zhang, W., Rutter, W.J., German, M. Transcriptional synergy between LIM-homeodomain proteins and basic helix-loop-helix proteins: the LIM2 domain determines specificity. *Mol. Cell. Biol.* 17:3488-3496 (1997).

24. Sander, M., Neubuser, A., Kalamaras, J., Ee, H. C., Martin, G. R., German, M. Genetic analysis reveals that PAX6 is required for normal transcription of pancreatic hormone genes and islet development. *Genes & Development* 11:1662-1673 (1997).

25. Goldfine, I. D., German, M., Tseng, H., Bolaffi, J., Chen, J.-W., Olson, D., Rothman, S. The endocrine secretion of human growth hormone and insulin by exocrine glands of the gastrointestinal tract. *Nature Biotech.* 15:1378-1386 (1997).

26. Sussel, L., Kalamaras, J., Hartigan-O'Connor, D. J., Meneses, J., Pedersen, R., Rubenstein, J., German, M. Mice lacking Nkx2.2 have diabetes due to an arrest in pancreatic  $\beta$ -cell differentiation *Development* 125: 2213-2221(1998).

27. Furuta, H., Hirokawa, Y., Iwasaki, N., Hara, M., Le Beau, M., Davis, E., Ogata, M., Iwamoto, Y., German, M., Bell, M.  $\beta$ -cell transcription factors and diabetes mellitus: mutations in the coding region of the BETA2/NeuroD (NEUROD1) and Nkx2.2 (NKX2B) genes are not associated with MODY in Japanese *Diabetes* 47: 1356-1358 (1998).

28. Sander, M., Griffen, S., Wang, J., German, M. A novel glucose responsive element in the human insulin gene promoter functions uniquely in primary cultured islets *Proc. Nat. Acad. Sci. USA* 95: 11572-11577 (1998).

29. Cabrera-Valladares, G., German, M., Matschinsky, F., Wang, J., Fernandez-Mejia, C. Effect of retinoic acid on glucokinase activity and gene expression in primary cultures of pancreatic islets *Endocrinology* 140:3091-3096 (1999).

30. Smith, S., Ee, H., Conners, C., German, M. Paired-homeodomain transcription factor PAX4 acts as a transcriptional repressor in early pancreatic development *Mol. Cell. Biol.* 19:8272-8280 (1999).
31. Romero-Navarro, G., Cabrera-Valladares, G., German, M., Matschinsky, F., Velazquez, A., Wang, J., Fernandez-Mejia, C. Biotin regulation of pancreatic glucokinase and insulin in primary cultured rat islets and in biotin deficient rats *Endocrinology* 140:4595-600 (1999).
32. Ohneda, K., Mirmira, R., Wang, J., Johnson, J., German, M. The homeodomain of PDX-1 mediates multiple protein-protein interactions in the formation of a transcriptional activation complex on the insulin gene promoter *Mol. Cell. Biol.* 20:900-911 (2000).
33. German, M. Insulin gene regulation. in *Diabetes Mellitus: a Fundamental and Clinical Text* (ed. LeRoith, D., Olefsky, J., and Taylor, S.) Lippincott-Raven Pub., Philadelphia, PA (2000).
34. Ohneda, K., Ee, H., German, M. Regulation of insulin gene transcription. *Seminars in Cell and Developmental Biology* 11:227-233 (2000).
35. Dreyer, S., Morello, R., German, M., Zabel, B., Winterpacht, A., Lundstrom, G., Horton, W., Oberg, K., Lee, B. LMX1B transactivation and expression in nail patella syndrome. *Human Mol. Gen.* 2000: 1067-1074 (2000).
36. Mirmira, R., Watada, H., German, M. Beta-cell differentiation factor Nkx6.1 contains distinct DNA-binding interference and transcriptional repression domains *J. Biol. Chem.* 275:14743-14751 (2000).
37. Schwitzgebel, V., Scheel, D., Conners, J., Kalamaras, J., Lee, J., Anderson, D., Johnson, J., German, M. Expression of Neurogenin3 reveals an islet cell precursor population in the pancreas *Development* 127:3533-3542 (2000).
38. Watada, H., Mirmira, R., Kalamaras, J., German, M. Intramolecular control of transcriptional activity by the NK2 specific domain in NK-2 homeodomain proteins *PNAS USA* 97:9443-9448 (2000).
39. Sander, M., Paydar1, S., Ericson, J., Briscoe, J., Berber, E., German, M., Jessell, T., Rubenstein, J. Ventral neural patterning by Nkx homeobox genes: Nkx6.1 controls somatic motor neuron and ventral interneuron fates *Genes & Development*, 14:2134-2139 (2000).
40. Watada, H., Mirmira, R., Leung, J., German, M. Transcriptional and translational regulation of  $\beta$ -cell differentiation factor Nkx6.1 *J. Biol. Chem.* 275: 34224-34230 (2000).
41. Horikawa, Y., Horikawa, Y., Cox, N., Iwasaki, N., Ogata, M., Iwamoto, Y., Schwitzgebel, V., German, M., Bell, G. Beta-cell transcription factors and diabetes: no evidence for diabetes-associated mutations in the coding region of the basic-helix-loop-helix transcription factor neurogenic differentiation 4 (*NEUROD4*) in Japanese patients with MODY. *Diabetes* 49:1955-1958 (2000).
42. Smith, S., Watada, H., Scheel, D., Mrejen, C., German, M. Autoregulation and MODY transcription factors control the human *PAX4* promoter. *J. Biol. Chem.* 275: 36910-36919 (2000).
43. Sander, M., Sussel, L., Conner, J., Schwitzgebel, V., Hayes-Jordan, A., German, M. Homeobox gene Nkx6.1 lies downstream of Nkx2.2 in the major pathway of beta-cell formation in the pancreas *Development* 127: 5533-5540 (2000).

44. Griffen, S., Wang, J., German, M. A genetic defect in beta-cell gene transcription segregates independently from the *Fa* locus in the ZDF rat. *Diabetes* 50:63-68 (2001).
45. del Bosque-Plata, L., Lin, J., Horikawa, Y., Schwarz, P., Cox, N., Iwasaki, N., Ogata, M., Iwamoto, Y., German, M., Bell, G. Beta-cell transcription factors and diabetes: no evidence for diabetes-associated mutations in the coding region of the proendocrine neurogenin 3 gene (*NEUROG3*) in Japanese patients with MODY. *Diabetes* 50:694-696 (2001)
46. Fernandez-Mejia, C., Vega, J., Rojas-Ochoa, A., Rodriguez-Dorantes, M., Romero-Navarro, G., Matschinsky, F., Wang, J., German, M. Cyclic AMP increases pancreatic glucokinase activity and gene expression *Endocrinology* 142:1448-52 (2001).
47. Lee, J., Smith, S., Watada, H., Lin, J., Scheel, D., Luukela, V., Wang, J., Mirmira, R., German, M. Regulation of the pancreatic pro-endocrine gene neurogenin3 *Diabetes* 50:928-36 (2001).
48. Thameem, F., Wolford, J. K., German, M. S., Bogardus, C. and Prochazka, M. Cloning, expression and genomic structure of human *LMX1A*, and variant screening in Pima Indians for Type 2 diabetes *Gene* 290:217-225 (2002).
49. Wilson, M., Kalamaras, J. and German, M. Expression pattern of IAPP and prohormone convertase 1/3 reveals a distinctive set of endocrine cells in the embryonic pancreas. *Mechanisms of Development* 115:171-6 (2002).
50. Lee, J., Wu, Y., Qi, Y., Xue, H., Scheel, D., German, M., Qui, M., Guillemot, F., Rao, M. Neurogenin3 participates in gliogenesis in the developing vertebrate spinal cord. *Developmental Biology* 253(1):84-98 (2003).
51. Wilson, M., Scheel, D., German, M. Gene expression cascades in pancreatic development. *Mechanisms of Development* 120(1):65-80 (2003).
52. German, M. Genetic regulation of islet function. in *Joslin's Diabetes Mellitus* (ed. Kahn, C.R., Jacobson, A., King, G., Moses, A., Smith, R., Weir, G.) *In press*.
53. German, M. Insulin gene regulation. in *Encyclopedia of Hormones* (ed. Henry, H. L. and Norman, A. W.) *in press*.
54. Masharani, U., Karam, J., and German, M., Pancreatic hormones and Diabetes Mellitus in Basic and Clinical Endocrinology, 7<sup>th</sup> Edition. (ed. Greenspan, F. and Gardner, D.) *in press*.
55. German, M. Insulin gene regulation. in *Diabetes Mellitus: a Fundamental and Clinical Text*, 3<sup>rd</sup> edition. (ed. LeRoith, D., Olefsky, J., and Taylor, S.) *in press*.
56. Fernandez-Mejia, C. and German, M. Regulation of glucokinase by vitamins and hormones. in *Glucokinase and Glycemic Diseases: From Basics to Normal Therapeutics*. (ed. Magnuson, M. and Matschinsky, F.) *in press*.
57. Watada, H., Scheel, D., Leung, J., German, M. Distinct gene expression programs function in progenitor and mature islet cells. *J Biol Chem* 278(19):17130-40 (2003).
58. Khoo, S., Griffen, S., Xia, Y., Baer, R. German, M., Cobb, M. Regulation of insulin gene transcription by extracellular-signal regulated protein kinases (ERK) 1 and 2 in pancreatic beta cells *Submitted*
59. Hald, J., Hjorth, J.P., Pedersen, E., Pedersen, J., German, M., Madsen, O., Serup P., Jensen, J. Activated Notch1 re-specifies endoderm to a pancreatic fate but blocks terminal

exocrine and endocrine differentiation. *Submitted*

60. Rulifson, I.C., Heiser, P.W., Swigart, L.B., Pelengaris, S., German, M., Gerard I., Evan, G. I., Bluestone, J. and Hebrok, M. Regulated  $\beta$  cell regeneration in the adult mouse pancreas. *Submitted*

61. Smith, S., Watada, H. and German, M. Neurogenin3 activates the islet differentiation program while repressing its own expression *Submitted*

62. Suzuki, R., Tobe, K., Terauchi, Y., Komeda, K., Kubota, N., Eto, K., Yamauchi, T., Azuma, K., Watada, H., Kawamori, R., Kajimoto, Y., German, M., Wright, C., Koga, T., Taguchi, T., Kimura, S., Nagai, R., and Kadowaki, T. Pdx-1 is not down-regulated in beta-cells from *Irs2*  $-/-$  mice. *Submitted*.

63. Smith, S., Gasa, R., Watada, H., Wang, J., Griffen, S. and German, M. Neurogenin3 and Hepatic Nuclear Factor 1 cooperate in activating pancreatic expression of Pax4. *Submitted*

64. Ogihara, T., Watada, H., Kano, R., Ikeda, F., Nomiyama, T., Tanaka, Y., Nakao, A., German, M., Kojima, I., Kawamori, R. p38 mitogen-activated protein kinase is involved in activin A- and HGF-mediated expression of proendocrine gene neurogenin3 in AR42J-B13 cells. *J. Biol. Chem.* In press.